UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,634	07/10/2001	Avi Ashkenazi	10466/67	1375

30313 7590 02/24/2003

KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 02/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/902,634	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 39-44 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 39-44 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

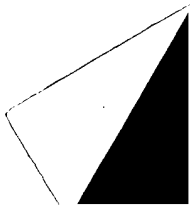
Status of the claims

1. Claims 39-44 are pending in the instant application

Claims 39-44 are under examination in the instant office action.

Sequence compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. Specifically, no sequence listing has been provided which includes the amino acid sequence presented in line 37 on page 2 and line 17 on page 14 of the instant specification. Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.



Oath/Declaration

3. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.The oath or declaration is defective because:

Perhaps, the printout of the declaration had a line shift, which resulted in misplacing address information as well as citizenship of each inventor. Therefore, in most cases the oath does not identify the mailing or post office address and citizenship of each inventor. A mailing or post office address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing or post office address should include the ZIP Code designation. The mailing or post office address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76.

4. Further, the oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration of inventor Wei-Qiang Gao. See 37 CFR 1.52(c).

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (page 71, line 28, for example). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

6. Tables 1-5 of the instant specification do not comply with 37 C.F.R. 1.52 (b) with respect to font size. 37 C.F.R. 1.52 (b) states that:

" Except for drawings, the application papers (specification, including claims, abstract, oath or declaration, and papers as provided for in this part) and also papers subsequently filed, must have each page plainly written on only one side of a sheet of paper, with the claim or claims commencing on a separate sheet and the abstract commencing on a separate sheet. See §§ 1.72(b) and 1.75(h). The sheets of paper must be the same size and either 21.0 cm. by 29.7 cm. (DIN size A4) or 21.6 cm. by 27.9 cm. (8 ½ by 11 inches). Each sheet must include a top margin of at least 2.0 cm. (3/4 inch), a left side margin of at least 2.5 cm. (1 inch), a right side margin of at least 2.0 cm. (3/4 inch), and a bottom margin of at least 2.0 cm. (3/4 inch), and no holes should be made in the sheets as submitted. The lines of the specification, and any amendments to the specification, must be 1 ½ or double spaced. The pages of the specification including claims and abstract must be numbered consecutively, starting with 1, the numbers being centrally located above or preferably, below, the text. See § 1.84 for drawings.
37 C.F.R. 1.58 (c) states that:

Chemical and mathematical formulae and tables must be presented in compliance with § 1.52(a) and (b), except that chemical and mathematical formulae or tables may be placed in a landscape orientation if they cannot be presented satisfactorily in a portrait orientation. Typewritten characters used in such formulae and tables must be chosen from a block (nonscript) type font or lettering style having capital letters which are at least 0.21 cm. (0.08 inch) high (e.g., elite type). A space at least 0.64 cm. (1/4 inch) high should be provided between complex formulae and tables and the text. Tables should have the lines and columns of data closely spaced to conserve space, consistent with a high degree of legibility.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 39, 40 and 44 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claims fail to include any limitations which would distinguish the claimed antibodies from those which occur in nature. In the absence of the hand of man, naturally occurring nucleic acid molecules and proteins are considered non-statutory subject matter. Diamond v.

Chakrabarty, 206 USPQ 193 (1980). Additionally, mere purity of a naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui, 156 USPQ 426 (1966). However, when purity results in a new utility, patentability is considered. Merck Co. v. Chase Chemical Co., 273 F. Supp. 68 (1967). Filing of evidence of a new utility imparted by the increased purity of the claimed invention and amendment of the claims to recite a purity limitation, if supported by the specification, is suggested to obviate this rejection. Applicant should point to the basis in the specification for any amendment to the claims.

8. Claims 39-44 are rejected under 35 U.S.C. 101 because the claimed invention is drawn to an invention with no apparent or disclosed specific and substantial credible utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. Because the instant application does not disclose the biological role of this protein or its significance, an antibody to the protein cannot be considered particularly useful.

It is clear from the instant application that the protein described therein is what is termed an "orphan protein" in the art. The DNA of the instant application has been isolated because of its similarity to a known DNA. There is little doubt that, after complete characterization, this DNA and encoded protein may be found to have a specific and substantial credible utility. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are

"useful" as it appears in 35 U.S.C. § 101, which requires that an invention must have either an immediate obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion".

The instant claims are drawn to an antibody that binds to a polypeptide of as yet undetermined function or biological significance. It is clear from the instant specification that the claimed antibody binds a novel polypeptide, designated PRO266 polypeptide and having amino acid sequence of SEQ ID NO: 91, which has homology to proteins containing leucine-rich repeats (page 12, first three paragraphs of the instant specification). More specifically, "it is [...] believed that PRO266 polypeptide disclosed in the present application is a newly identified member of the leucine rich repeat family and possesses ligand-binding activity and neuronal development typical of this family. SLIT has been shown to be useful in the study and treatment of Alzheimer's disease, supra, and thus, PRO266 may have involvement in the study and cure of this disease " (page 102, last two lines and page 103, lines 1-3, emphasis added). Thus, based on the structural similarities to different known proteins with known or proposed function, it has been suggested that the PRO266 of the instant invention would also possess similar biological activity. Numerous publications exist on a topic of predicting protein functions from structural similarities or homology to the known proteins. It is well described in the art that amino acid structure cannot necessarily predict the function of the protein: "Knowing the protein structure

by itself is insufficient to annotate a number of functional classes and is also insufficient for annotating the specific details of protein function" (see Skolnick et al., Box 2 on page 36 and the whole paper). Moreover, "Structural similarity does not necessarily mean a common evolutionary origin and homologous sequences may evolve into different folds (according to current classification schemes) (See Bork et al., Current Opinion in structural Biology, 1998, 8, page 332, first column, second paragraph). Thus, according to the state of the art, functional characteristics of a protein cannot be unequivocally extrapolated from its structural characteristics. Because the various members of the family of proteins containing leucine-rich repeats have diverse and different biological activity, including protein-protein interactions and neuronal development (page 12, third paragraph), one cannot predict that a protein of the instant invention will possess any particular activity based solely upon its structural similarity to the SLIT protein from Drosophilae, a member of this family.

The instant specification fails to provide any evidence or sound scientific reasoning that would support a conclusion that the instant polypeptide is associated with any diseases or disorder, including Alzheimer's disease, as asserted in the instant specification (page 103, line 2). Examples 74 and 77 of the instant specification (pages 208-209 and 210, respectively), which present information about the ability of PRO266 to stimulate the proliferation of stimulated T-lymphocytes and induce inflammation in skin vascular permeability assay fail to provide logical explanation how these data lead to the assertion of specific and substantial utility of the antibodies to PRO266 in the study and treatment of Alzheimer's disease. In the absence of knowledge of the biological significance of this specific polypeptide of SEQ ID NO: 91, there is

no immediately obvious patentable use for this polypeptide and, consequently, for the antibody that binds to it.

Further, to employ the anti-PRO266 antibodies of the instant invention "in diagnostic assays for PRO, e.g., detecting its expression in specific cells, tissues, or serum", as suggested in the instant specification (page 146, lines 33-34) is not a "real world" because it would eventually relate to a protein for which no biological function is known. The instant application also fails to demonstrate use of the antibodies as markers for any disease or condition (which would be a real world use). Because the instant specification does not teach a biological activity of the protein, one cannot prevent or treat a condition or disease as implied by the specification by delivering anti-PRO266 antibodies formulated as immunoliposomes (page 145-146, sections 8 and 9). . To employ the claimed antibody of the instant invention in any of the disclosed methods would clearly be using it as the object of further research, which has been determined by the courts to be a utility, which, alone, does not support patentability. Since the instant specification does not disclose a credible "real world" use for the claimed antibody, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 U.S.C. § 101 as being useful.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 39-44 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a clear asserted utility or a well established

utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claim 44 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 44 is directed to an antibody that binds specifically to the polypeptide of SEQ ID NO: 91. The instant specification fails to describe an antibody that specifically binds to a polypeptide of SEQ ID NO: 91 to the exclusion of binding to any other protein, for example, other human proteins or other proteins in general. There is no information provided, which would allow one skilled in the art to depict all possible amino acid sequences that lack specific epitopes accountable for specific binding to a polypeptide of SEQ ID NO: 91. There is no knowledge in the prior art that would provide guidance for one skilled in the art on how to exclusively distinguish polypeptides that lack specific epitopes of a polypeptide of SEQ ID NO: 91. There are no working examples that illustrate how to generate an antibody that binds exclusively to a polypeptide of SEQ ID NO: 91 and does not bind to any other polypeptide. Therefore, it would require undue experimentation and making extensive inventive contribution for one skill in the art in order to practice the currently claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claim 44 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 is vague and indefinite for recitation of "specifically binds to". The metes and bounds of the recitation cannot be determined form the claim or the instant specification because it is not clear if the specificity is defined by binding to a specific epitope, or to a protein from a particular species, or both.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mochly-Rosen et al. (US Patent 5,519,003). Only a copy of the first page of this reference will be forwarded to Applicant since it is believed to be too voluminous and easily obtainable.

Claim 39 encompasses an antibody which binds to the polypeptide of SEQ ID NO: 91. Mochly-Rosen et al. disclose an amino acid sequence which comprises an epitope of six contiguous amino acids, which completely match an epitope of SEQ ID NO: 91, see a copy of an alignment printout attached to the instant office action. Therefore, an antibody which binds to an epitope of a fragment of Mochly-Rosen et al. would anticipate the instant claims.

Mochly-Rosen et al. do not expressly disclose an antibody to this particular fragment of the polypeptide. However, at the time the invention was made it would have been *prima facie* obvious to one of ordinary skill in the art to produce an antibody to a fragment of a polypeptide disclosed by Mochly-Rosen et al. to permit the detection of that polypeptide in a sample. That antibody would be the same antibody that is encompassed by claim 39.

Conclusion

13. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D.
February 21, 2003

JOHN ULM
PRIMARY EXAMINER
GROUP 1800